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Effector mechanisms and their induction in *Trypanosoma cruzi* infection

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Infection with the parasitic protozoan *Trypanosoma cruzi* results in a chronic syndrome known as Chagas disease. The sites of disease in infected hosts, normally the heart and gut, are characterized by the persistence of intracellular parasites and inflammatory cells which ultimately result in cumulative tissue destruction and the compromise of organ function. The immune system in mammals is exposed to two distinct life cycle stages during the course of *T. cruzi* infection - extracellular trypomastigotes which circulate in the blood, and intracytoplasmic amastigotes, which are able to replicate in a wide variety of host cell types. Immune control of the infection is complex, minimally involving the contribution of antibodies, $CD4^+$ T cells and $CD8^+$ T cells. Using gene knockout and TCR transgenic mouse strains, we have examined the effector mechanisms important in cell mediated immunity to *T. cruzi*. Not surprisingly, immune control is best mediated by a strongly biased type 1 cytokine production pattern on the part of both $CD4^+$ and $CD8^+$ T cells. With respect to $CD8^+$ cells, the available data suggest that IFN-gamma production is critical but that cytolytic activity is a less important factor in the anti-parasite response mediated by these effector cells. How IFN-gamma acts is not yet clear but does not appear to depend on nitric oxide production by target cells.

Given this level of knowledge of immune control mechanisms in *T. cruzi* infection, we have focused our current studies on two primary questions: 1) why is *T. cruzi* able to persist despite the generation of a potent and multifaceted immune response? and 2) can the immune response be potentiated through vaccination to obtain more effective control of the infection and a reduced severity of disease? In examination of the question of parasite persistence, we have begun a study of the development and maintenance of the parasite-specific T cell responses throughout the course of the infection. In addition, we have examined the role of immune evasion mechanisms in persistence and have preliminary data supporting a role for altered peptide ligands in the regulation of responses to prominent parasite antigens.

Vaccination experiments using a small cocktail of parasite genes have provided proof of principle that prophylactic and therapeutic vaccination can enhance immune control and moderate the severity of disease. Future studies along these lines will attempt to determine specifically how vaccination alters the course of the immune response and thus the course of infection and disease. Moving beyond proof-of-principle experiments, we are also developing strategies to efficiently identify vaccine candidates which could be part of a genetic vaccine cocktail.